RESPONSE: We appreciate the comments of Drs. Kaye and Hill on our article. We are pleased that these investigators concurred with our impression that photodynamic therapy (PDT) may potentially be useful in the treatment of posterior fossa tumors. Several interesting questions were raised about the technical aspects of our method of determining tissue Photofrin levels in tumor and surrounding normal brain. Our laboratory concurs with their feelings about the limitations of relative fluorescence. We have therefore conducted additional investigations with radiolabeled Photofrin to quantify tissue levels by yet another technique.

The biodistribution of ^{111}In-Photofrin was determined in animals with brain tumors from the same canine glioma cell line used in the currently published studies. The tumor to nontumor ratio ranged between 6.45 and 7.16, at times ranging from 24 to 72 hours after injections. Radioactivity in brain and tumor tissue was detected using a Packard multisample autogamma counter (Cobra) with five gamma detectors. It is also of note that our ratios of target to nontarget (tumor to nontumor brain) Photofrin uptake agree with the published results of Origitano, *et al.*,[2] in which patients with glioblastoma demonstrated target to nontarget ratios of Photofrin uptake ranging from 2.5 to 10.4. We feel that our subsequent animal model studies and the published patient data of Origitano, *et al.*, confirm our previously published data on Photofrin uptake in the presently quoted preclinical study.

We believe that Drs. Kaye and Hill make an appropriate point about assessing possible thermal effects of laser irradiation using the treatment protocol we described in the current study. We, too, shared this concern during our experiments and placed intratumor temperature thermistors during each laser irradiation session adjacent to the spherical diffusion tip of the fiberoptic catheter. In no situation was there a significant temperature rise recorded by this thermal probe. We were not satisfied, however, because of our concern over tissue heating. We therefore conducted additional studies in which we used laser-only controls in comparison to PDT in order to document possible thermal effects from the laser point source. In such controls, a small defect was revealed on magnetic resonance imaging (pathologically/histologically confirmed) at the tip of the fiberoptic catheters, which was possibly due to thermal effects not demonstrated using our temperature probe. We have subsequently carried out additional experiments in dogs using even lower doses of laser light and the balloon adapter technique described by Muller and Wilson[1] to provide between 33 and 100 J/sq cm. We have succeeded in treating residual malignant brain tumor tissue directly adjacent to the brain stem with markedly reduced neurotoxicity if the lower light dose and the lower (0.75 mg/kg) Photofrin dose was utilized. Survivable brain-stem toxicity (resolving hemiparesis) occurred with this technique in a dog so treated.

Our model using a canine glioma cell line in the posterior fossa location and a single fiber laser irradiation technique was not intended to convince readers that this is the best method of future treatment for human posterior fossa brain tumors using PDT. Our model was intended to be more scientifically rigorous, treating brain tumors with only one therapeutic modality, thus not combining the results of surgical resection with those of photodynamic effect. We therefore feel that our ability to treat posterior fossa brain tumors near the brain stem with a technique such as ours, which does not minimize the possible cerebral edema or tumor burden by prior surgical resection, constitutes a worst-case scenario. Therefore, any survivability in our animal model with objective evidence of a therapeutic response constitutes an intellectually honest assessment of the PDT regimen, without confounding variables. Use of resection, balloon techniques with intracavitary irradiation, or multiple fiber techniques, among others may certainly improve upon therapeutic efficacy and control of neurotoxicity in human clinical applications.

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